INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 00-CH-0219 PRINCIPAL INVESTIGATOR: Carolyn A. Bondy, M.D.

STUDY TITLE: Turner Syndrome: Genotype and Phenotype

Continuing Review Approved by the IRB on 5/27/09
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Adult with Turner Syndrome

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Nature of the Study

You have a condition called Turner syndrome. We invite you to participate in this clinical research study to evaluate the clinical and genetic (inherited) factors related to Turner syndrome. During this study, we will compare the genotype (specific genes each individual carries) with the phenotype (specific physical and mental characteristics of each individual) in individuals with Turner syndrome.

Genotype refers to the entire genetic makeup of an individual. Phenotype refers to a group of traits or characteristics, resulting from both genes and the environment. Our genes provide the messages that instruct the cells of our bodies what to do and when to do it. Our genes are responsible for the color of our eyes and hair, our height, our development, and many other things. We all have genes that we inherit from our parents, which are located on our chromosomes. These chromosomes are rod-like structures in all the cells of our body. Most cells in the body contain 22

pairs of chromosomes called autosomes and one pair of sex chromosomes. The X chromosome represents one of the sex chromosomes, of which women normally have two copies.

Turner syndrome is a common genetic problem, affecting one out of every 2500 females. Those with Turner syndrome often have a single X chromosome, or one normal and one defective X chromosome. X chromosome problems can cause some abnormal physical characteristics, such as a webbed neck, low set ears, and heart or kidney defects. X chromosome defects may also lead to short stature, lack of sexual development, and ovaries that do not work properly. Until now, most studies of Turner syndrome have focused on pediatric problems such as short stature and delayed or absent puberty. Recently, it has been noted that adult women with Turner syndrome have a much higher risk for developing medical problems such as high blood pressure, diabetes mellitus and osteoporosis (fragile bones) than women of the same age who do not have X-chromosome defects. It is not known whether these health problems are due to specific, X-chromosome related genetic problems, or to absent or inadequate ovarian hormone effects.

We hope to identify the specific X-chromosome genes that cause many of the medical problems in girls and women with Turner syndrome. By learning more about the genes that cause this disorder, we hope to improve the diagnosis and treatment of individuals with Turner syndrome, and possibly women's health problems in general.

Research Tests and Procedures for this Study

If you enroll in this study, you will be admitted to the Clinical Center of the National Institutes of Health for a 3-5 day stay. While you are in the hospital, we plan the following studies:

1. Physical examination, including a look at the breasts and private (genital) area to assess how much puberty (teen-age development) has occurred. With your permission, we would also like to photograph any abnormal findings, such as a low hairline or a low set of ears. This will help us to document certain abnormal traits found in individuals with Turner syndrome.

2. Body measurements will be taken, including sitting and standing height, weight, and hip and waist measurements. These will be made using a scale and a flexible tape measure.

3. Blood drawing. Blood will be collected for blood count, liver function, kidney function, ovary hormones, growth factors, thyroid function, clotting factors, heart disease risk factors (cholesterol etc.), bone strength markers, vitamin and mineral levels, a genetic analysis of chromosomes, and research. The research blood will be stored at this medical center for later use in case there are new ways to measure bone markers or hormone levels in the future. The amount of blood taken will be approximately 12 table spoonfuls (180 ml), which is within the standard safety guidelines for studies at the National Institutes of Health. This guideline allows for drawing up the same amount as would be permissible for donation to a blood bank (one pint every six weeks for adults).

4. Diet. While in the Clinical Center you will be given a regular diet (unless you have a medical condition requiring a special diat), meaning meals designed to contain adequate salt and carbohydrate to allow accurate testing of your blood pressure and glucose metabolism.

5. Glucose tolerance tests:
Oral. There is a high incidence of diabetes and problems with carbohydrate metabolism in females with Turner syndrome. We would like to find out if you have these problems. An oral glucose tolerance test will be done in order to evaluate this. In preparation for the test, you will not eat or drink anything but water for about 12 hours prior to the test. You will be

given a sugary drink (Glucola) to drink. A small amount of blood (about 2 tablespoons total) will be drawn to measure insulin sensitivity prior to the drink and afterwards at 4 separate times. The test will take about 3 hours to complete. A heparin lock (a catheter with small plastic tubing) will be inserted into a vein in your arm. This will avoid the discomfort of having a needle stick several times in order to draw blood samples.

7. Urinalysis. A small container will be given to you to collect a urine sample.

8. Electrocardiogram (ECG). Individuals with Turner syndrome have been reported to have an increasing frequency of heart and blood vessel problems. As part of the evaluation of your heart, we would like to do an electrocardiogram (ECG). This test is painless. It involves removing your shirt and having small electrodes (sticky patches) applied to your chest. Wires will be connected to the electrodes and a machine will produce the paper readout. ECGs are pictures of the electrical conduction of your heart. It helps us to find abnormalities in the heart.

9. X-rays of the wrists will be taken for the evaluation of wrist deformities, which have been found in some individuals with Turner syndrome.

10. DEXA scan (dual energy x-ray absorptiometry). One of the reasons that some individuals with Turner syndrome have problems with diabetes and carbohydrate metabolism may be that they have excess fat and too little muscle in their bodies. We would like to measure your body composition by doing a DEXA x-ray study. Also with this same study, we can measure bone thickness. This is important to evaluate because individuals with Turner syndrome are reported to have a high bone fracture rate. One of the reasons for this may be that those with Turner syndrome do not achieve fully developed bones.

The DEXA scan measures body fat, muscle, and bone thickness. This procedure involves lying on a flat table while a very small dose of x-rays are passed through the body. The total time required to stay in the imager will be determined by the doctor performing the examination, but we estimate this will take, at most, one hour. At all times, you will be able to communicate with the technologist operating the machine and others in the room. You may come out of the imaging device at any time you request. There is no discomfort or physical pain involved.

11. A Magnetic resonance imaging (MRI) study will be done to evaluate your heart for any defects. MRI does not use x-rays. You will lie on a stretcher in a large tube. This tube is in the middle of a strong magnet, which is used to take pictures. For this reason, it is very important that you do not wear anything with metal in it or any jewelry inside the MRI machine. You may not be able to have a MRI test done if you have any metal inside your body, such as metal rods, pins, heart valves, pacemakers, or defibrillators. If so, notify your doctor prior to going to MRI, because there is a risk of the metal moving. During the MRI, a rhythmic tapping sound from the machine can be heard during the study. The total time spent in the MRI will be decided by the radiologist performing the study, but we estimate that it will take about 1 hour. At all times, you will be able to talk with the technologist operating the machine through a two-way microphone. You may come out of the MRI at any time requested. There is no discomfort or physical pain.

Some people become claustrophobic (fear of enclosed spaces) while in the machine. The tube is open at both ends, but there is not much room for movement. If you have a tendency to become claustrophobic, we can give you an anti-anxiety medication prior to the test to help with relaxation.

You may, during the course of the MRI examination, receive an injection in your vein of a solution containing Gadolinium-DTPA (GD-DTPA). This solution is a commonly used MRI "contrast agent." It is called a "contrast agent" because it changes the relative brightness – the contrast on the MRI image of those parts of the body in which it accumulates (before being excreted). This improves the visibility of abnormalities on the MRI scan and the value of the MRI scan in the diagnosis of disease and in the planning of any treatment needed.

12. Quantitative CT scan. Individuals with Turner syndrome often report frequent broken bones. We want to study how strong your bones are to see why this happens. You will have a Quantitative CT scan of your lower spine. CT, which stands for computerized tomography, is an x-ray procedure enhanced by a computer. It produces a three-dimensional view of a particular part of your body. This test will measure the bone mineralization of your lower spine and the amount of fat located in the abdominal region. The exam usually takes about 30 to 60 minutes. This includes preparation time and time for the computer to generate the image. The actual exposure time is about 15 minutes. You will be placed on a narrow scanning table and secured into position with a belt. It is very important not to move during the scanning, because even the slightest movement can lead to blurry pictures. You will be moved into the scanner, which is open at both ends. A technologist will be able to see and hear you at all times through a window and a two-way microphone system. You will hear a humming of the equipment while it is taking pictures. There is little discomfort and no pain involved.

13. Echocardiogram. Since heart defects are relatively common in Turner syndrome, we want to evaluate your heart to see if you have this problem. An echocardiogram test makes images of the heart through the use of sound waves. This painless test can help to identify abnormalities in the heart muscle and valves. You will be asked to remove all clothing from the waist up. Three electrodes will be attached to your chest to record an ECG at the same time. Conduction gel will be applied to the chest area. You will lie on a bed and may be asked to move into different positions. As the nurse/technologist presses a probe to the chest area, several readings and images will appear on the video screen. When all the needed information is obtained, the gel and electrodes will be removed. This is a painless and risk-free test.

14. Blood pressure measurements. High blood pressure may also be common in Turner syndrome. We want to study your blood pressure to see if you have this problem. Nurses on the unit will do blood pressure measurements every 8 hours while you are in the hospital. You will also be given a portable arm cuff unit for ambulatory 24-hour blood pressure recording. We will teach you how to apply and use the unit.

15. Ear exam and Hearing testing. Individuals with Turner syndrome often have problems with their hearing and with frequent ear infections. We want to evaluate your hearing and ears to see if there are any problems in these areas. A specialist will examine your ears and test your hearing. There will be no pain involved. Prior to the ear exam, a nurse will wash out any wax from your ear canals with warm water if necessary. This evaluation will take about 30-45 minutes.

16. Neurocognitive tests. (Select subjects with 46X, Xp or Xq deletions karyotype) Some individuals with Turner syndrome may have difficulty with nonverbal memory and visual-perceptual abilities. We are trying to learn about features of that Turner syndrome related to brain function and learning ability. We may ask you to complete some computerized tests and questionnaires. These tests measure spatial ability and nonverbal learning abilities. This evaluation will take 4-5 hours. Because this is a research evaluation, this information will not be added to your medical record, and therefore will not become part of her permanent record. All research psychological evaluations will be kept in locked files.

17. Renal and Pelvic Ultrasound. Some individuals with Turner syndrome have abnormalities of their kidneys and/or their ovaries. For this reason, we would like for you to have a renal and pelvic ultrasound in order to examine your kidneys, uterus and ovaries. All ultrasounds are performed in the Radiology Department, but they do not involve the use of x-rays. To do the test, a transducer will be used. This is a hand-held device with a rounded tip. It emits sound waves into your body, then returns the echo to a monitor. You will be asked to lie on an exam table. Gel will be put on the skin over the body area to be scanned. The gel makes the skin smooth so that the transducer can move easily over your skin. This exam will last approximately 30 - 45 minutes.

18. Parents' DNA. With your permission, we will contact your parents in order to obtain saliva samples for DNA extraction from them. Their DNA samples will be analyzed and compared with yours to examine how inherited traits are passed from one generation to the next. This may help us to better understand how and why certain traits of Turner syndrome are expressed.
During our research, we may uncover information about relationships in the family. For instance, we may learn that a child is not the biological child of the parents with whom the child lives. This information is generally not shared with any family members or physicians, except in extreme circumstances. Such a circumstance would include the medical care of involved individuals. In this case, the information is provided to the health care provider.

19. Skin Biopsy. A few individuals may be asked to undergo a skin biopsy to obtain more information about the genetic make-up of different populations of cells. This is a routine procedure, which allows us to study cells known as fibroblasts that we can culture from skin. An area of skin is numbed with a local anesthetic (numbing medicine) such as Lidocaine. A very small circular area is then removed using a special skin punch and scissors. This is a sterile procedure. The site is then covered with a bandage or small strips of tape. The wound heals quickly, usually within a week. You may decline this test, without affecting participation in the rest of the protocol.

20. Liver ultrasound and possible biopsy. Many women with Turner syndrome have abnormal liver function the cause and consequences of which are unknown at present. To clarify this issue and determine if any potentially treatable liver disorder exists, we measure liver enzymes and image the liver with ultrasound. Adults who have liver abnormalities may be asked to undergo a liver biopsy. This would involve enrolling in another research protocol entitled "Evaluation of patients with liver disease". All the risks and discomforts associated with liver biopsy are described in detail in the consent for that protocol, which you will be asked to sign if you decide to take part in this procedure.

21. Heart CT scan & Angiogram: Women with Turner syndrome appear to have an increased number of risk factors for coronary heart disease and for vascular abnormalities. Therefore, we will use a sensitive, low radiation CT scan to

examine the coronary arteries that supply oxygen to your heart. During the CT angiogram scan, you will receive a "contrast agent" through your intravenous catheter. Since the heart moves as you breathe, we will ask you to hold your breath intermittently for about 5-20 seconds. To slow your heart rate you may receive a medication called a "beta blocker". You will be placed on a narrow scanning table and secured into position with a belt. It is important that you remain still since the slightest movement can lead to blurry pictures. The scanner is open on both ends. A technologist will be able to see and hear you at all times through a window and a two-way microphone system.

22. Holter Monitoring: Women with Turner syndrome appear to have an increased heart rate and/or other heart rhythm disturbances. To determine if these heart rhythm disturbances are associated with Turner Syndrome, a Holter monitor will be used over several hours to 24 hours to monitor your heart beat. The Holter monitor is a portable ECG. Like the ECG, the Holter monitor has leads which are placed on your chest to trace the electrical conduction of your heart. This is a non-invasive, painless procedure.

23. Applanation tonometry: Since women with Turner syndrome often have cardiovascular defects, we want to investigate the arterial wall for structural or functional abnormalities. For this test we use applanation tonometry which is a non-invasive, painless procedure used to test aortic blood pressure and arterial stiffness. Your BP is taken and an ECG lead is placed on your ankle and wrist. While the ECG is recording, a high-fidelity pencil-sized meter is placed first on the neck artery (carotid), then the wrist artery (radial) and finally the upper leg artery (femoral). The entire procedure takes approximately 15minutes.

24. Autonomic nervous system telemetry: To evaluate the activity of the nervous system in controlling heart rate and BP in Turner syndrome, we will measure the heart rate, breathing rate and blood pressure over a period of about 15 min while you are seated in a comfortable chair. Sticky electrodes similar to those used in running an ECG will be placed on your collar bones and lower rib cage (you may remain clothed). A blood pressure cuff will be placed on your upper arm. You will be asked to sit quietly, take some deep breaths, relax, take a breath and bear down while holding the breath (Valsalva test), relax, and finally to stand upright. There are no known risks to the test. Some individuals may find it uncomfortable to sit relatively still for 15 min and some individuals might feel dizzy for a moment when standing upright at the conclusion of the test. A doctor and nurse will be present during the test to make you as comfortable as possible.

25. Peripheral Insertion of a Central Catheter (PICC) placement: As an alternative to the heparin lock, we may place a PICC line into your vein for blood sampling. A PICC line is a long IV catheter that is place into your arm with the tip of the catheter located in the large vein above the heart. This prevents trauma to the vein from multiple venous sticks and allows for easier blood testing. The potential complications are the same as an IV line or a heparin lock. They include possible bleeding or bruising at the site, pain or infection.

26. Occupational functioning and vocational functioning testing: We would like to study women's impressions of their roles, how successfully they engage in occupations important to them, how they approach and adapt to professional life in the context of having Turner syndrome. You will be evaluated by a trained specialist in occupational therapy and vocational rehabilitation. The evaluation will be in the form of a personal interview and questionnaires. This will be done in 3 separate sessions, each with approximate length 30 to 60 minutes.

Longitudinal aspect of the study:
We may ask willing participants to return at 2-5 year intervals (up to 15 years) to re-evaluate glucose metabolism using the oral glucose tolerance test and aortic diameter and function using the MRA. We will also evaluate your thyroid and liver function through blood testing (about 1 tsp.) In addition, any unusual or new medical problems identified during the initial visit or arising later may be addressed. This testing may be completed in 1-2 days in the clinic or day hospital.

Risks and Discomforts:

You will be asked to discontinue taking non-essential medications two weeks prior to admission: these may include estrogen, growth hormone, vitamins, herbal remedies, cholesterol-lowering medications, and medications to prevent or treat osteoporosis. These medications could interfere with the blood and urine testing that will be done during the study. The study investigators will go over your medications with you and your doctor before admission to decide which if any should be stopped. You should not discontinue any medications unless specifically instructed to do so by a study investigator or by your own doctor. You will be able to restart your medications once the study is completed. In general, the discontinuation of these types of medications for a short period of time should not cause any harm, however you should consult with your primary care giver to determine if it will be advisable for you. You may experience some side effects when discontinuing medications, such as hot flashes when discontinuing estrogens. If you experience any side effects that are not tolerable while off of the medications, you should contact your primary care giver. You may have to go back on your medications again. If you are not able to discontinue these medications, you will still be able to participate in this study.

Physical Examination: A physician will examine you with your clothes off. Your privacy will be protected, but some patients may find this examination embarrassing.

There is the discomfort and inconvenience of blood and urine collection. The risks to blood collection are minimal but include the possibility of bruising, discomfort, or inflammation at the site of the needle puncture. In some cases, fainting may occur. Appropriate treatments will be offered if these rare complications occur. The risk of "low blood" resulting from the blood collection is minimal, because the amount of blood taken will be maintained within the standard guidelines for studies at the National Institutes of Health. This guideline allows for drawing up the same amount as would be permissible for donation to a blood bank (one pint every six weeks for adults). The total blood collected for this study will be about 6 ounces. This amount of blood is within the allowable amount according to the NIH safety guidelines. Urine collection is not risky, but it is inconvenient because of the time required for collection.

There may be some discomfort and inconvenience to the oral glucose tolerance test. The risks to having a heparin lock placed and having blood drawn are minimal, but include the possibility of bruising, discomfort, inflammation, or infection at the site of the needle insertion. The sugar water drink may sometimes cause headache, stomachache, or nausea. However, these side effects will be relieved within a short period of time.

There are no risks of having an electrocardiogram (ECG) or echocardiogram done. There is the inconvenience of having to disrobe from the waist up, having gel and sticky electrodes placed on the chest, and the time it takes to complete the tests. There may be minimal discomfort as the ball of the probe is pressed to the chest during the echocardiogram. This discomfort will go away when the test is complete.

There is also no risk of having the autonomic nervous system telemetry done. Some individuals may find it uncomfortable to sit still for 15minutes and some individuals might feel dizzy for a moment when standing upright at the conclusion of the test. Any discomfort will go away once the test is completed.

This research study involves exposure to radiation from x-rays, CT scans, and DEXA scans. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation you will receive in this study is from the following procedures: an x-ray of both wrists, a Quantitative CT scan of your lower spine**,** heart CT and CT angiogram and DEXA scans of your wrist, hip, spine, and whole body. The NIH radiation

Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving slightly greater than minimal risk and necessary to obtain the research information desired.

Using the standard way of describing radiation dose, from participating in this study, you will receive a total of 7.6 rem to your breast, 6.0 rem to your lungs, and 3.0 rem to your esophagus as well as 3.0 rem to your thymus gland. All other organs will receive smaller amounts of radiation.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of the effective dose **1.7 rem**. This calculated value is known as the effective dose and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guidelines established by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem (or 5,000 mrem) received per year.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive material that are found naturally in the earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive 6 years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet call, *An Introduction to Radiation for NIH Research Subjects*.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose, even low doses such as those received during this research.

One possible effect that could occur as a result of the radiation exposure in this study is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation exposure received from this research study is 0.07 percent. Therefore, the total risk of fatal cancer may be estimated to increase from 25 percent to 25.07 percent. This additional risk is too small to be measured and is generally regarded as insignificant.

Please advise your doctor if you have participated in research studies at the NIH or other institutions that involved the use of radiation so that we can ensure that the total radiation dose from all studies is not too much. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

MRI is not painful, but may be inconvenient because of the time needed to complete the study. Approximately 1 out of 100 people are too claustrophobic (scared of small spaces) to have MRI. During the scanning, you will hear a rhythmic tapping sound due to the switching on and off of the gradient coils. Most people find the sound only mildly objectionable. Ear plugs will be provided if requested. The long-term effects of MRI on the body are unknown. However, there is no evidence at this time of any harmful effects.

Gadolinium and CT contrast media are FDA approved medication used to improve MRI and CT images. Experience with a large number of patients has shown the contrast agent (Gd-DPTA) to be safe and without side effects in the majority of patients. The most common reactions are coldness in the arm at the time of injection of the agent, headache, mild abdominal distress, and nausea. Each of these reactions lasts for a short period of time and occurs in about 0.5% of patients. More severe reactions (shortness of breath, wheezing, or lowering of the blood pressure) have occurred in an extremely small number of patients, 10 in 1.5 million. Gadolinium can cause a complication called Nephrogenic Systemic Sclerosis which presents either immediately or up to one year after the administration of the dye. The manifestations include stiffness of the skin and muscles and can affect internal organs and even be fatal. However this complication has been found only in individuals with impaired kidney function. It is unknown if it occurs in individuals with normal kidney function. We will not administer Gadolinium to any study participant whose tests indicate a possible kidney insufficiency. Renal, liver or abdominal ultrasounds do not cause any pain or discomfort. There is no radiation exposure with this procedure.

The beta blocker is given to slow your heart rate for the purpose of getting clear pictures of your heart during the CT. In a small number of patients, this medication resulted in excessive slowing of the heart rate, lowering of blood pressure, narrowing of the airways or an allergic reaction. These events are more likely to occur if there is a preexisting condition such as asthma. You will not be given this medication if you have any of the conditions which may cause such adverse effects.

There are no known risks to the neurocognitive testing, occupational functioning testing and vocational functioning testing. However, it may be tiring and inconvenient due to the amount of time needed for testing. Some participants may feel initially uncomfortable detailing how they perform a range of personal, social and school/work related activities.

Some discomfort and risks are associated with the skin biopsy. There is mild discomfort with the injection of the local anesthetic. Following the injection, there should be no further discomfort. Risks include bleeding, reaction to the local anesthetic, and infection. We will monitor the site for any sign of such problems, which may be easily treated. The biopsy is generally taken from the inside of the forearm. A small scar will develop, which normally fades over time. You may decline this test if you wish, without interfering with participation in the remainder of the protocol.

Potential Benefits

By participating in this study, you may help health care professionals and others learn more about the genetic causes of the various clinical features in Turner syndrome. You will benefit from a very thorough medical evaluation, which may help to uncover unsuspected problems that you may have. Once these problems are discovered, prevention strategies and treatment plans can be explored in order to strive towards better health outcomes. You will have an opportunity to discuss the results of all your tests and evaluations and current knowledge about Turner syndrome with the study investigators. By taking part in this study, you might also help other patients with Turner syndrome benefit from improved diagnosis and treatment in the future. Refusal to participate in this study will have no impact on your care or participation in other protocols.

Other General Issues Related to the Protocol

1. **Treatment/Compensation**. There will be no financial payment to you for your participation. Travel will be paid for those who meet NICHD guidelines for such payment. Treatment will not routinely be provided for conditions identified during the NIH evaluation. However, abnormal results will be communicated to participants and their doctors.

2. **Confidentiality.** The clinical and genetic information collected in this study will be entered into a secure Turner syndrome database, which will be used to compare specific traits and specific genes in patients with Turner syndrome. Only protocol investigators will have access to this database. All information entered into this database will be coded, so that you cannot be identified by name, except by the principal investigator. All psychological and cognitive evaluations for research will be kept in locked files by study investigators. All information obtained from this research that can be identified with you will remain confidential within the limits of the law. Such private information will be released only to the investigators and the NIH. Representatives from the NIH may review and photocopy your medical and research records. The results of this research may appear in scientific publications without identifying you by name.

A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. This protection, however, does not prohibit the investigator from voluntarily reporting information. For example, if we learn something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help.

3. **Unanticipated medical information.** During the course of our research, it is possible that we will learn unexpected information regarding your health or genetic background. If this information is important to your health, we will share the information with you or your health care provider.

4. **Genetic analysis**. Using the cells from a blood sample or skin biopsy, we will separate out a substance called DNA. This will be used to look for genes related to Turner syndrome and its phenotype. Samples will be stored for possible future genetic analyses related to X chromosome abnormalities. It will not be used for other purposes. The DNA material used for these analyses will not be linked to your name. We will protect your identity by substituting your name on the DNA specimen with a code. In this way, none of the people involved in the analysis of your DNA will know that it belongs to you.

5. **Evaluation results**. All subjects participating in this study will be informed of the results of their evaluations in detail, and will be provided with written summaries of results. All subjects will be given the opportunity to discuss the results of their tests with study investigators.

ALTERNATIVES TO PARTICIPATION

If you do not wish to participate in this study, we can refer you to other centers where Turner syndrome is investigated.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Carolyn Bondy, M.D.; Building CRC, Room 1-3330, Telephone: (301) 496-4686 or the Lead Associate Investigator Vladimir Bakalov, M.D. (301) 496-3883.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 27, 2009 THROUGH MAY 26, 2010.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____